Exhibit A

Clinical study results for Controlled Release Oxycodone/Naloxone Formulations

1. Objective

The primary objective of this study was to investigate whether an oxycodone/naloxone combination in accordance with the invention will lead to a comparable analgesia with a decrease in constipation in patients with severe chronic pain of tumour and non-tumour origin, and need for laxatives, when compared with oxycodone alone. A further objective was to investigate which dose ratio of oxycodone to naloxone was the most effective and most suitable for further development with respect to bowel function improvement, analgesic efficacy, and safety. A third objective was to compare the incidence of other side effects between treatment groups.

The method for the assessment of bowel function and analogue scales for use in this method were employed in a clinical Phase II study conducted in Europe.

2. Test Population, Inclusion and Exclusion Criteria

In total 202 patients were randomized and 152 patients were to receive both naloxone and oxycodone; 50 patients were to receive oxycodone and naloxone placebo. The Intent to Trial (ITT) population consisted of 196 (97,0%) patients. The Per Protocol (PP) population consisted of 99 (49%) patients.

Study participants were selected according to inclusion and exclusion criteria. In general, male or female patients, aged $\geq$ 18 years, suffering from severe chronic pain of tumour and non-tumour origin and who required opioid treatment were enrolled in the study. Patients with insufficient efficacy or tolerability to WHO II or III analgesic and patients with stable oxycodone therapy (40 - 80 mg/day) were suitable for screening. Patients included in the double-blind treatment period were on stable oxycodone treatment and had a medical need for the regular intake of laxatives.

Patients were selected according to the following inclusion criteria.

Inclusion Criteria

- Aged ≥ 18 years
- with severe chronic pain of tumour and non-tumour origin that required opioid treatment
- and/or insufficient efficacy with a WHO II or III analgesic
- and/or insufficient tolerability with a WHO II or III analgesic
- or patients under current stable oxycodone therapy (40 - 80 mg/day)
- were capable of voluntary participation and of providing written informed consent
- could understand the requirements of the protocol and were willing and able to fulfil them.

Patients who were to be included in the maintenance treatment period (maintenance face) and titration or run-in were those:

- on stable oxycodone treatment 40 - 80 mg/day with no more than 5 rescue medication intakes (oxycodone) per week
- with the medical need for the regular intake of laxatives to have at least 3 bowel evaluations/week

Exclusion Criteria

Patients were to be excluded from the study where those:

- with current alcohol or drug abuse
- with current severe cardiovascular and respiratory disease (e.g. lung cancer and metastases)
- with current severe liver and renal insufficiency (transaminases threefold above normal range) and/or liver/renal carcinoma and/or metastases
- with a history of paralytic ileus
- with current acute pancreatitis
- with a history of psychosis
- with a history of Morbus Parkinson
- in the process of taking early disease-related retirement
- receiving another opioid treatment besides oxycodone

- with a known hypersensitivity to one of the study drugs
- which participated in another clinical study within 30 days of study entry
- were female and pregnant or lactating
- were female of child bearing potential and not adequately protected against conception

Specifics of the test population can be taken from Figures 1 and 2.

3. Test Treatment, Dose, and Mode of Administration

Preparations administered

Tablets of dosage strengths 20 mg oxycodone, 10 mg oxycodone, 5 mg naloxone and 10 mg naloxone were prepared by spray granulation. Oxycodone dosage strengths of 30 mg were administered by using one 10mg dosage strength tablet and one 20 mg dosage strength tablet. Oxycodone dosage strengths of 40 mg were administered by using two 20mg dosage strength tablets.

Oxycodone Hydrochloride PR Tablets 10 mg

Oxycodone hydrochloride PR tablets 10 mg are round, biconvex, white film coated tablets with OC on one side and 10 on the other. The composition of oxycodone hydrochloride PR tablets 10 mg is given below:

Composition of Oxycodone Hydrochloride PR Tablets 10 mg

Constituents	mg/tablet	Function	Reference to Standard
Tablet Core			
Active constituent			
Oxycodone hydrochloride[1] (Oxycodone base equivalent)	10.00 (9.00)	Active Ingredient	Ph Eur
Other constituents			
Lactose monohydrate (spray-dried lactose)	69.25	Diluent	Ph Eur
Povidone (K 30)	5.00	Binder	Ph Eur
Ammonio methacrylate copolymer dispersion (Eudragit RS 30 D)[2] (solids)	10.00	Retardant	USP/NF

Triacetin	2.00	Plasticiser	Ph Eur
Stearyl alcohol	25.00	Retardant	Ph Eur
Talc	2.50	Glidant	Ph Eur
Magnesium stearate	1.25	Lubricant	Ph Eur
Total core weight[3]	130		

Film Coat

Opadry white Y-5R-18024-A[4]	5.00	Coating	
Purified water[5]	-	Solvent	Ph Eur
Total tablet weight	135		

Film Coat Composition

The approximate composition of a 5 mg film coat is as follows:-

Component			
Hypromellose 3 mPa.s (E464)	1.750	Film former	Ph Eur
Hypromellose 50 mPa.s (E464)	0.250	Film former	Ph Eur
Hydroxypropylcellulose	1.500	Film former	Ph Eur
Titanium Dioxide (E171)	1.000	Colorant	Ph Eur
Macrogol 400	0.500	Plasticiser	Ph Eur

1 Anhydrous basis. Batch quantity is adjusted for assay/ moisture content.

2 Eudragit RS 30 D consists of a 30% dispersion of ammonio methacrylate copolymer NF (Poly [ethylacrylate-co-methylmethacrylate-co-(2-trimethyl ammonio ethyl) methacrylate chloride] {1:2:0.1) NF) in purified water Ph Eur, preserved with 0.25% (E,E)-Hexa-2,4-dienoic acid (sorbic acid) Ph Eur/NF

3 Includes ~4% residual moisture i.e. 5 mg per tablet core.

4 Actual quantity of coat is about 5 mg. Coat is applied to the core tablets to obtain a 3-4% weight increase and a uniform appearance.

5 Removed during processing.

Oxycodone Hydrochloride PR Tablets 20 mg

Oxycodone hydrochloride PR tablets 20 mg are round, biconvex, pink film coated tablets with OC on one side and 20 on the other. The composition of oxycodone hydrochloride PR tablets 20 mg is given below.

Composition of Oxycodone Hydrochloride PR Tablets 20 mg

Constituents	mg/tablet	Function	Reference to Standard
Tablet Core			
Active constituent			
Oxycodone hydrochloride[1] (Oxycodone base equivalent)	20.0 (18.00)	Active Ingredient	Ph Eur
Other constituents			
Lactose monohydrate (spray-dried lactose)	59.25	Diluent	Ph Eur
Povidone (K 30)	5.00	Binder	Ph Eur
Ammonio methacrylate copolymer dispersion (Eudragit RS 30 D)[2] (solids)	10.00	Retardant	USP/NF
Triacetin	2.00	Plasticiser	Ph Eur
Stearyl alcohol	25.00	Retardant	Ph Eur
Talc	2.50	Glidant	Ph Eur
Magnesium stearate	1.25	Lubricant	Ph Eur
Total core weight[3]	130		
Film Coat			
Opadry Pink YS-1R-14518-A[4]	5.00	Coating	
Purified water[5]	-	Solvent	Ph Eur
Total tablet weight	135		

Film Coat Composition

The approximate composition of a 5 mg film coat is as follows:-

Component			
Hypromellose 3 mPa.s (E464)	1.5625	Film former	Ph Eur
Hypromellose 6 mPa.s (E464)	1.5625	Film former	Ph Eur
Titanium Dioxide (E171)	1.4155	Colorant	Ph Eur
Macrogol 400	0.4000	Plasticiser	Ph Eur
Polysorbate 80	0.0500	Wetting agent	Ph Eur
Iron oxide red (E172)	0.0095	Colorant	HSE

1 Anhydrous basis. Batch quantity is adjusted for assay/ moisture content.

2 Eudragit RS 30 D consists of a 30% dispersion of ammonio methacrylate copolymer NF (Poly [ethylacrylate-co-methylmethacrylate-co-(2-trimethyl ammonio ethyl) methacrylate chloride] {1:2:0.1) NF) in purified water Ph Eur, preserved with 0.25% (E,E)-Hexa-2,4-dienoic acid (sorbic acid) Ph Eur/NF

3 Includes ~4% residual moisture i.e. 5 mg per tablet core.

4 Actual quantity of coat is about 5 mg. Coat is applied to the core tablets to obtain a 3-4% weight increase and a uniform appearance.

5 Removed during processing.

Naloxone Tablets

Naloxone prolonged release tablets, are controlled release tablets using a matrix of stearyl alcohol and ethyl cellulose as the retardant. The tablets contain 10 mg naloxone hydrochloride per tablet. The complete statement of the components and quantitative composition Naloxone prolonged release tablets is given below.

Naloxone prolonged release tablets

Component		Quantity (mg/tablet)		Function	Reference to Standard
	Nal 5mg	Nal 10mg	Nal 15mg		
Naloxone hydrochloride Dihydrate	5.45	10.90	16.35	Active	Ph. Eur.*
corresponding to					
Naloxone hydrochloride anhydrous	5.00	*10.00*	15.00		
Naloxone base	4.50	*9.00*	13.50		
Povidone K30	5.00	5.00	5.00	Binder	Ph. Eur.*
Retarding Suspension (Surelease E-7-7050) (dry mass) comprising	10.00	10.00	10.00		
1. Ethylcellulose	6.93	6.93	6.93	Retardant	Ph.Eur.*
2. Dibutyl Sebacate	1.60	1.60	1.60	components	U.S.N.F *
3. Oleic Acid	0.77	0.77	0.77	of the release	U.S.N.F.*
4.Colloidal anhydrous silica	0.70	0.70	0.70	controlling matrix	Ph.Eur.*
Stearyl alcohol	25.00	25.00	25.00	Retardant	Ph. Eur.*
Lactose monohydrate	74.25	69.25	64.25	Diluent	Ph. Eur.*
Purified talc	2.50	2.50	2.50	Glidant	Ph. Eur.*
Magnesium stearate	1.25	1.25	1.25	Lubricant	Ph. Eur.*
TOTAL TABLET WEIGHT	**123.0**	**123.0**	**123.0**		* current Edition

Study design

The clinical study was conducted in Germany as a multi-center, prospective, controlled, randomized, double-blind (with placebo-dummy), four group parallel study with oral controlled release (CR) oxycodone, oral controlled-release (CR) naloxone and corresponding naloxone placebo.

The total study duration was up to 10 weeks, including a screening period, a minimum two week titration period (maximum 3 weeks) (or a one week run-in period), a four week treatment period (oxycodone and naloxone/naloxone placebo) and a follow-up phase of two weeks.

Patients with stable pain control, who fulfilled all inclusion/exclusion criteria were randomized to double-blind therapy in one of three naloxone treatment groups or a naloxone placebo treatment group.

The study had three core phases: a pre-randomization phase, a 4-week double-blind treatment period (maintenance phase) and a follow-up phase. The pre-randomization phase consisted of screening and titration/run-in. Following screening, patients entered either a titration or run-in period. Patients with insufficient pain pre-treatment entered a minimum 2-week titration period and were individually titrated and stabilized at an oxycodone dose of 40 mg, 60 mg or 80 mg per day. Patients on stable oxycodone pre-treatment at screening (between 40-80 mg/day) and with concomitant constipation, entered a 1 week run-in period and were eligible for the maintenance phase without prior titration. For all patients, the dose of oxycodone could be adjusted during titration or run-in and investigators maintained compulsory telephone contact every 2nd day to assess pain control and make dose changes.

At the end of the titration/run-in period, patients who were receiving a stable maintenance dose of 40 mg, 60 mg or 80 mg oxycodone per day (with no more than 5 rescue medication intakes per week) and had a medical need for the regular intake of laxatives were randomized to one of 3 naloxone treatment groups or a naloxone placebo treatment group. Each patient received their maintenance dose of oxycodone plus either 10 mg, 20 mg, 40 mg or naloxone placebo CR tablets daily (see Table 2).

After the treatment period, patients maintained their maintenance dose of oxycodone only for a further two-week follow-up phase (40 mg, 60 mg, or 80 mg oxycodone per day). Patients maintained a daily diary, and efficacy and safety assessments were performed over the course of the study.

Table 1: Treatment groups for maintenance phase based on naloxone dose per day.

	Group 1	**Group 2**	**Group 3**	**Group 4**
Naloxone daily dose (mg)	Placebo **0**	5 + 5 **10**	10 + 10 **20**	20 + 20 **40**
Oxycodone daily dose (mg)	2x20, 2x30, 2x40 **40 60 80**	2x20, 2x30, 2x40 **40 60 80**	2x20, 2x30, 2x40 **40 60 80**	2x20, 2x30, 2x40 **40 60 80**

Oxycodone + Naloxone dose (mg)	**40/pl 60/pl 80/pl**	**40/10, 60/10, 80/10**	**40/20, 60/20, 80/20**	**40/40, 60/40, 80/40**
Ratio	40/pl 60/pl 80/pl	4/1, 6/1, 8/1	2/1, 3/1, 4/1	1/1, 1.5/1, 2/1

Note: Identical dose ratios were obtained for 40/10 mg and 80/20 mg (4/1) and for 40/20 mg and 80/40 mg (2/1)

202 subjects were randomized, 196 were in the ITT populations and 166 completed the study. The study design schematic for the clinical study is displayed in Figure 3.

Blinded naloxone CR tablets (5 mg and 10 mg) were supplied in bottles. The dosage regimen was constant for the entire double-blind treatment period and no dose adjustments were allowed. Patients received 5, 10 or 20 mg of oral naloxone each morning and evening.

Open label oxycodone CR tablets (10 mg and 20 mg) were supplied in PP blisters. Dose adjustments could be performed during the titration/run-in period and 10 mg CR oxycodone tablets were available as rescue medication throughout the entire study. The dosage regimen was constant for the entire double-blind treatment period. Patients received 20, 30 or 40 mg of oral oxycodone each morning and evening.

Blinded naloxone placebo tablets were optically identical to naloxone tablets 5 mg and 10 mg. Dose and mode of administration were as for naloxone CR tablets.

The Intent-To-Treat (ITT) population included all randomized patients who received at least one dose of study drug and had at least one post-randomization efficacy assessment. For some analyses, the last observation was carried forward for those ITT subjects who discontinued after Visit 4 (ITT/LOCF). In other instances, only the available data were used (ITT non-missing).

The Per Protocol (PP) population included all randomized patients who completed the study (including the follow-up phase) without major protocol violations. Major protocol violations were defined as:

- Patients who received more than 50 mg oxycodone per week as rescue medication during the maintenance phase or did not follow one of the scheduled oxycodone dose regimens (40 mg, 60 mg or 80 mg oxycodone per day).
- Less than 4 morning and 4 evening assessments of mean pain intensity were documented during the last 7 days prior to each visit.
- Very large deviations from the scheduled visits, i.e. the date of visit was outside the respective visit window. Only deviations from the visit window of the maintenance phase visits (visit 4 and 5) were regarded as major protocol violations. Deviations from the other visits were regarded as minor protocol violations. For the identification of a major protocol violation, the visit windows for visit 4 and 5 were slightly increased after a blinded review of the data and were defined as follows:
  - visit 4 (during the maintenance phase):
  - visit 3 plus 6 to 12 days
  - visit 5 (at the end of the maintenance phase):
  - visit 3 plus 25 to 31 days.

4. Primary Efficacy Variables

Efficacy assessments were determined based on data recorded in the case report form and in patient diaries.

The primary efficacy variables of interest were pain and bowel function as follows:

a) Mean Pain during the last 7 days prior to each visit, based on the patient's twice-daily assessment of pain intensity using the 0-100 numerical analogue scale (NAS) (0= no pain and 100= worst imaginable pain). Mean Pain was calculated for each study visit as the mean value of the daily mean values of all patient's diary entries from the last 7 days.

b) Mean bowel function: patient's assessment, at each study visit, of bowel function during the last 7 days prior to each visit. Mean bowel function was calculated from the mean of the three 0-100 NAS scores: ease of defecation (0= easy/no difficulty, 100= severe difficulty), feeling of incomplete bowel evacuation (0= not at all, 100= very strong), and judgment of constipation (0= not at all, 100= very strong).

Secondary efficacy variables of interest included among others:

c) Global assessment of efficacy, tolerability and preference. Evaluation for global assessment of efficacy was measured using a 0 to 7 numerical analogue scale (1 = very good, 2 = good, 3 = pretty good, 4 = moderate, 5 = slightly poor, 6 = poor, 7 = very poor). Tolerability was measured using the same 0 to 7 numerical analogue scale. Preference was measured by assessing preference for maintenance (oxycodone/naloxone combination) or titration/run-in (oxycodone only) regarding efficacy/tolerability of study medication using a 0 to 3 NAS (1 = titration/run-in, 2 = maintenance, 3 = no preference).

For the global assessment of efficacy, tolerability and preference summary statistics for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio were provided for the ITT population.

d) Laxative intake/mean laxative dose, which was calculated from the respective case report forms (CRF) entries. An analysis of the mean laxative dose during the last seven days was performed for patients who took only one laxative during the entire study. Entries from the medication record CRF page were used for all calculations (laxatives were identified by the WHO ATC Code A06A). For laxative intake number of days with laxation during the last 7 days and the percentage of days with laxation during the last 7 days were calculated for each study visit. In addition, the percentage of days with laxation during the whole maintenance phase and during the follow-up phase was calculated.

e) Subjective symptoms of withdrawal (SOWS), which were recorded daily by the patient in the diary during the first seven days of the maintenance phase included: I am anxious; I have to yawn; I am sweating; My eyes are watering; My nose is running, I have gooseflash; I am shivering; I feel hot; I feel cold; My bones and muscles are aching; I am restless; I feel sick; I have to vomit; My muscles are twitching; I have abdominal cramps; I cannot sit still. All symptoms were rated as "0 = not at all", "1 = little", "2 = medium", "3 = strong" or "4 = extreme".

SOWS were recorded during the first 7 days of the maintenance phase in the patient diary. For the additional post-hoc analysis, the total score (= sum score) of the SOWS items was calculated for each patient and day. Additionally for each patient, the minimum, mean and

maximum of the 7 daily dose scores were calculated. These parameters were summarized via simple characteristics for each oxycodone/naloxone ratio and absolute naloxone dose.

Safety assessments were determined based on data recorded in the case report form and in patient diaries.

Safety assessments consisted among others of monitoring and recording all adverse events (AEs).

f) An adverse event was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, including placebo, and which did not necessarily have a causal relationship with treatment. Therefore, an adverse event could be

- an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product whether or not considered to be related to the medicinal product,
- any new disease or acerbation of an existing disease,
- any detoriation in non-protocol-required measurements of laboratory value or other clinical test that resulted in symptoms, a change in treatment or discontinuation from study drug.

Assessment of causality in suspected adverse events in response to a medicinal product was based on the following considerations: Associated connections (time or place); pharmacological explanations; previous knowledge of the drug; presence of characteristic, clinical or pathological phenomena; exclusion of other causes and/or absence of alternative explanations. The causal relationship to the study drug was assessed using a classification ranging from 0 to 4 (0 = not related: temporal relationship to drug administration is missing or implausible, 1 = improbable: temporal relationship to drug administration makes a causal relationship improbable, and other drugs, chemicals or underlying disease provide plausible explanations; 2 = possible: reasonable time sequence to administration of the drug, but event could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawal may be lacking or unclear; 3 = probable: reasonable time sequence to administration of the drug, but unlikely to be attributed to concurrent disease or other drugs or

chemicals, and which follows the clinically reasonable response on withdrawal (dechallenge), rechallenge information is not required; 4 = definite: plausible time relationship to drug administration; event cannot be explained by concurrent disease or other drugs or chemicals; the response to withdrawal of the drug (dechallenge) should be clinically plausible; the event must be definitive pharmacologically or phenomenologically using a satisfactory rechallenge procedure, if necessary). All adverse events during the course of the study were all collected on the adverse event CRF. Elicited adverse events (nausea, emesis, abdominal pain, cramping, diarrhea, sedation, vertigo, headache, sweating, restlessness, skin reactions (pruritus, urticara and other)) and volunteered adverse events were documented (pain and constipation were not classified as adverse events for the study).

All analysis except the elicited opioid typical and naloxone typical adverse events analysis were performed for the safety population. The elicited opioid typical and naloxone typical adverse events analysis were performed on the ITT population as they were previously considered for be efficacy analysis. Adverse events were summarized by absolute number and percentage of patients, who

- had any adverse events,
- had an adverse event in each defined system organ class,
- experienced each individual adverse event.

The sum score of the severity of elicited opioid typical or elicited naloxone typical adverse events was calculated for each study visit as the sum of the scores assigned to each of the above-mentioned adverse events absolved during the last 7 days. A score of 0 was assigned, if the respective side-effect was not observed during the last 7 days, a score of 1, if the adverse event was mild, a score of 2, if the adverse event was moderate, and a score of 3, if the adverse event was severe. If for one side-effect more than one adverse event with different severities were recorded during the last 7 days, the worst severity was used.

Summary statistics for the sumscore of the severity of elicited opioid typical and elicited naloxone typical adverse events during the last 7 days were provided for each study visit for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio. In addition, Wilcoxon tests (modified to handle the Behrens-Fischer problem) of absolute dose of naloxone versus

placebo were performed in the ITT population for values at Visit 4 (after 1 week of naloxone treatment) and for values at the end of the maintenance phase (after 4 weeks of naloxone treatment).

Additional summary statistics were provided for the sumscore of the severity of elicited opioid typical and elicited naloxone typical adverse events during the whole maintenance phase for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio, and for the sumscore of the severity of elicited opioid typical and elicited naloxone typical adverse events during the follow-up phase by absolute dose of oxycodone. This analysis was performed using the ITT population.

Adverse events, as mentioned above, were identified by the following the Medical Dictionary for Regulatory Affairs (MeDRA). Elicited opioid-typical adverse events were considered to be nausea, emesis, sedation, skin reactions, as identified in the aforementioned MeDRA (leading to a maximum sum scor of 12). Elicited naloxone-typical adverse events were considered to be abdominal pain, cramping and diarrhea with the definitions applied as laid out in MeDRA (leading to a maximum sum scor of 9).

5. Analgesic Efficacy Results

The end of maintenance mean pain results are summarized below:

Table 2: Mean Pain at End of Titration Visit (V3) and End of Maintenance Visit (V5) by Absolute Dose of Naloxone - ITT (with non-missing data) and PP Analysis Populations.

Population	Statistic	Naloxone Placebo	Naloxone 10 mg	Naloxone 20 mg	Naloxone 40 mg
ITT non-missing	N	46	42	43	41
	Mean (SD) V3	36.9 (15.9)	35.9 (16.3)	39.8 (18.4)	38.1 (15.8)
	Mean (SD) V5	37.8 (18.2)	37.2 (17.3)	37.5 (20.5)	38.7 (17.0)
	95% Confidence Interval for Difference vs. Placebo*		(-5.04, 4.58)	(-2.36, 7.22)	(-4.76, 4.93)
PP	N	29	26	22	22

	Mean (SD) V3	34.0 (16.0)	38.0 (17.7)	40.1 (20.0)	39.0 (16.1)
	Mean (SD) V5	32.6 (16.6)	38.8 (18.4)	36.1 (19.5)	38.7 (16.6)
	95% Confidence Interval for Difference vs. Placebo*		(-9.10, 2.94)	(-5.01, 7.64)	(-8.41, 4.22)

*95% Confidence Intervals for Difference vs. Placebo at Visit 5 (end of maintenance) are based on an ANCOVA model with treatment and baseline pain intensity as factors in the model.

The differences were small and confidence intervals were fairly narrow relative to the 0-100 pain scale and did not point to a difference in analgesic efficacy between active naloxone and naloxone placebo.

Thus, in the ITT population mean pain scores (±SD) ranged from 38.3 (±18.49) to 38.8 (±16.59) compared to 36.9 (±15,74) for placebo during the last 7 days prior to visit 4 and 37.2 (±17.24) to 38.7 (±17.05) compared to 37.8 (±18.22) for placebo during the last 7 days at the end of the maintenance phase. Analgesic efficacy did not change at V4 and V5 with oxycodone dose or oxycodone/naloxone ratio in a quadratic response surface model using oxycodone dose and the ratio as factors and baseline mean pain as covariant.

A quadratic response surface model with naloxone and oxycodone dose as factors and baseline pain as covariant shows that the only factor that affects the end of maintenance mean pain is the baseline pain measurement. There was no evidence of changes in mean pain with varying amounts of naloxone. However the study was not designed nor powered as a formal demonstration of non-inferiority of oxycodone/naloxone versus oxycodone/naloxone placebo.

6. Bowel Function Efficacy Results

Mean bowel function was calculated for each study visit from the mean of the three NAS values ease/difficulty of defecation, feeling of incomplete bowel evacuation and judgment of constipation. Summary statistics for mean bowel function during the last 7 days were provided for each study visit for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio.

To test for difference of absolute dose of naloxone versus placebo, t-tests were performed for the values obtained during the end of maintenance phase (after 4 weeks of naloxone treatment). In addition, two-sided 95% CIs (CI, confidence interval) for the difference in means between the treatment groups were provided. A response surface analysis was also performed for the end of the maintenance phase (after 4 weeks of naloxone treatment). These analyses were performed for the ITT and PP populations. For the ITT population only, t-tests for difference were also performed to explore mean bowel function at Visit 4 (after 1 week of naloxone treatment).

In addition, summary statistics of mean bowel function during the last 7 days for the end of the follow-up phase were provided for the grouping absolute dose of oxycodone in the ITT population.

To evaluate the effects of the titration/run-in period a paired t-test for difference was conducted for the mean bowel function during the last 7 days before the end of titration/run-in, compared with the mean bowel function during the last 7 days before the baseline visit. This analysis was performed in the titration phase population. In addition, two-sided 95% CIs for the difference in means between the treatment periods were provided.

Figures were provided for the ITT and the PP population. The values obtained for mean bowel function during the last 7 days before the end of the maintenance phase (mean ± 95% CI) were plotted against the oxycodone/naloxone dose ratio and the absolute dose of naloxone. In addition, surface plots were provided for the results obtained at the end of the maintenance phase.

To investigate if the bowel function depends on the ratio of oxycodone and naloxone or the absolute dose of naloxone additional analysis and figures were provided for the ITT population. A response surface analysis for the total consumed oxycodone dose during the last week of the maintenance phase versus the naloxone dose was performed. The parameter estimates derived were taken to display a surface plot of the whole dose range investigated. Moreover, a contour plot of the bowel function with a granulation of 10 was performed.

The values for mean bowel function at each study visit by dose ratio, by absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio in

the ITT population are presented in Figures 4 to 6. The test for difference for each dose of naloxone versus placebo is summarized in Figure 7.

The surface plot of the whole dose range investigated based on the RSREG estimations of the model parameters is displayed in Figure 8. The contour plot of the bowel function with a granulation of 10 is shown in Figure 9.

Within the ITT population, a trend towards improved mean bowel function with increased dose of naloxone was seen. During the last 7 days at the end of the maintenance phase, mean (±SD) bowel function was lowest in the 1/1, 1.5/1 and 2/1 dose ratios (21.9±22.25, 21.8±21.35 and 26.7±23.98 for the 1/1, 1.5/1 and 2/1 dose ratios, respectively). Furthermore, mean bowel function worsened as the amount of naloxone decreased, to a maximum value of 47.8 (±23.20) for a dose ratio of 6/1. For the last 7 days prior to Visit 4, mean bowel function ranged from 20.7 (±19.24) at a ratio of 1/1 to 45.7 (±26.86) at a ratio of 8/1 (see Figure 4). Values for mean bowel function in the oxycodone/naloxone placebo dose ratios were higher than in the 1/1, 1.5/1 and 2/1 dose ratios at both visits.

Analysis by absolute dose of naloxone showed values of 45.4 (±22.28), 40.3 (±23.09), 31.3 (±25.82) and 26.1 (±25.08) for placebo, 10 mg, 20 mg and 40 mg respectively at the end of maintenance ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo, t-test for difference) and 43.3 (±26.41), 42.1 (±25.53), 34.2 (±30.04) and 27.9 (±22.68) at Visit 4 ($p=0.004$ for 40 mg naloxone versus placebo, t-test for difference) (see Figures 5 and 7).

Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio showed that within both dose ratio groups (4/1 and 2/1) patients taking the higher oxycodone dose had higher mean bowel function values at Visits 4 and 5 (see Figure 6).

From the end of the maintenance phase to end of follow-up, mean bowel function worsened. The range for mean bowel function was 21.8 (±21.35) to 48.2 (±21.71) for the dose ratio groups at end of maintenance and 33.2 (±20.76) to 52.1 (±26.79) for the dose ratio groups at the end of follow-up. The change was greatest in the 40 mg naloxone group; mean bowel function was 26.1 (±25.08) at the end of maintenance and 42.4 (±23.19) at the end of follow-up.

Analysis using the PP population generally mirrored the trends observed in the ITT population with regards to mean bowel function. During the last 7 days at the end of the maintenance phase, mean (±SD) bowel function was lowest in the 1/1 dose ratio (10.7±15.35) and worsened to a maximum of 57.3 (±17.38) for a dose ratio of 6/1. Mean bowel function values were higher than the 1/1, 1.5/1 and 2/1 ratios for all oxycodone/placebo dose ratios. Similar values were seen for the last 7 days prior to Visit 4 with the exception of the 3/1 dose ratio. At the end of the maintenance phase mean bowel function was 42.3 (±24.03), 39.4 (±23.44), 29.8 (±29.29) and 29.6 (±28.34) for placebo, 10 mg, 20 mg and 40 mg naloxone. The small number of patients in each treatment group in the PP population meant statistically significant p-values were not obtained in the PP analysis for t-tests for difference for mean bowel function.

The end of maintenance mean bowel function results are summarized below:

Table 3: Mean Bowel Function Scores at End of Titration Visit (V3) and End of Maintenance Visit (V5) by Absolute Dose of Naloxone - ITT (non-missing) and ITT/LOCF Analysis Populations.

Population	Statistic	Naloxone Placebo	Naloxone 10 mg	Naloxone 20 mg	Naloxone 40 mg
ITT non-missing	N	45	41	42	40
	Mean (SD) V3	48.2 (23.5)	53.5 (22.2)	51.3 (21.6)	48.2 (20.6)
	Mean (SD) V5	45.4 (22.3)	40.3 (23.1)	31.3 (25.8)	26.1 (25.1)
	P-Value*		0.1658	0.0025	0.0002
ITT / LOCF	N	48	47	47	42
	Mean (SD) V3	47.7 (24.0)	53.6 (22.8)	49.9 (23.1)	47.7 (20.5)
	Mean (SD) V5	44.8 (22.9)	40.1 (24.7)	33.2 (28.4)	26.5 (25.7)
	P-Value*		0.1795	0.0140	0.0005

*Comparison versus Naloxone Placebo using ANCOVA model with Naloxone dose and baseline bowel function as factors in the model.

As already mentioned above, within the ITT population, improved mean bowel function with increased dose of naloxone was seen, with mean values (± SD) of 45.4 (±22.3), 40.3 (±23.1), 31.3 (±25.8) and 26.1 (±25.1) for placebo, 10 mg, 20 mg and 40 mg respectively at the end of maintenance ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo). The 95% confidence intervals for the mean bowel function differences from naloxone placebo were (-2.83, 16.69) at 10 mg naloxone, (5.46, 24.82) at 20 mg naloxone, and (9.54, 29.11) at 40 mg naloxone.

The results display an increasing improvement in bowel function with increasing dose of naloxone, with the difference of the 20mg and 40mg dose versus naloxone placebo statistically significant at end of maintenance.

The response surface quadratic analysis confirms improving bowel function with increasing dose of naloxone, with the linear effect of naloxone dose statistically significant. The Table 5 displays the estimated improvements in mean bowel function scores versus naloxone placebo for the different oxycodone/naloxone ratios studied; these estimates correspond both to oxycodone/naloxone combinations actually represented in the study design, and some combinations for which quadratic surface interpolation was appropriate.

The estimates indicate that the mean bowel function improvement is in general constant within each ratio, and independent of the varying doses of oxycodone and naloxone. The only possible exception is the 80/40 mg combination, where there is a suggestion of a lower predicted effect than for the 60/30 mg and 40/20 mg combinations; this observation, however, has to be interpreted with the size of the standard error in mind.

Table 4: Response Surface Analysis of Bowel Function Efficacy by Oxycodone Dose and Oxycodone/Naloxone Ratio (Estimated Improvement (SE) vs Naloxone Placebo).

Oxycodone dose / **ratio Oxycodone/Naloxone**	40 mg Oxycodone/day	60 mg Oxycodone/day	80 mg Oxycodone/day
4:1	10.2 (3.7)	11.8 (4.3)	11.0 (5.6)
3:1	13.1 (4.5)	14.5 (4.8)	12.5 (6.3)
2:1	18.0 (5.7)	18.2 (4.9)	12.4 (7.7)

In addition to estimating the treatment effect for individual oxycodone/naloxone combinations, overall treatment effect estimates were obtained for specific ratios. The estimates were calculated by combining the results from the different oxycodone/naloxone combinations, e.g.; the 2:1 ratio estimate was formed by averaging the predicted results of the 40/20 mg, 60/30 mg, and 80/40 mg oxycodone/naloxone combinations, relative to naloxone placebo. The estimated mean differences (SE) in mean bowel function for various oxycodone/naloxone ratios versus naloxone placebo groups are displayed below.

Table 5: Response Surface Analysis of Bowel Function Efficacy by Oxycodone/Naloxone ratio (Estimated Improvement (SE) vs Naloxone Placebo).

Oxycodone / Naloxone Ratio	**Overall Improvement (SE) vs Placebo**
6:1	8.0 (3.3)
4:1	11.1 (4.1)
3:1	13.4 (4.6)
2:1	16.2 (4.5)
1.5:1	16.5 (5.1)

The estimates indicate that bowel function improvement increases as oxycodone/naloxone ratio decreases, with the estimated improvement at 2:1 approximately 50% higher than at 4:1 ($p < 0.05$) and with a minimal improvement from the 2:1 ratio to the 1.5:1 ratio.

It was thus shown, that the 2/1 and the 1.5/1 ratios demonstrated significant differences compared to the corresponding oxycodone dose plus naloxone placebo at V4 and V5. The oxycodone/naloxone combination provided improvements in ease of defecation, feeling of incomplete bowel evacuation and judgement of constipation. The greatest improvements were seen at dose ratios of 1/1, 1.5/1 and 2/1.

7. Global Assessment-Efficacy, Tolerability and Preference-Results

The results for the global assessment of efficacy, tolerability and preference are shown in Figs. 10 to 13. The 1/1 dose ratio was ranked good or very good by more patients and investigators than any other dose ratio. In total, 73.3% of investigators and 66.6% of patients rated the efficacy of the 1/1 dose ratio as good or very good. The 2/1 dose ratio was ranked good or very good by 50.4% of investigators and 59.4% of patients.

A similar trend can be observed for tolerability of medication with 86.7% of investigators and 80% of patients rating the tolerability of the 1/1 dose as good or very good. High ratings were also observed in the 80 mg placebo dose ratio group (81.3% for investigators and 68.8% for patients), 8/1 dose ratio (77.3 for both investigators and patients) and 2/1 dose ratio (68.7% for investigators and 68.8% for patients).

For global preference, the maintenance phase was preferred by the majority of investigators and patients for the 1/1 dose ratio. This was supported by the results obtained in the naloxone 20 mg and 50 mg treatment groups. For naloxone placebo, the distribution of preference between titration, maintenance and no preference was generally even regarding efficacy and tolerability.

8. Subject Opioid Withdrawal Scale Results

Subjects were asked to report the occurrence of opioid withdrawal in their diaries during the first week of treatment with naloxone. These were assessed by rating the above-mentioned 16 symptoms on a scale of 0 (not at all) to 4 (extremely). A total SOWS score ranging from 0 to 64 was computed by summing-up the scores across the 16 symptoms.

The mean sum scores for SOWS are indicated in Table 6 below.

Table 6: Mean sum score for SOWS

Mean Score	40 mg Placebo N=17	60 mg Placebo N=17	80 mg Placebo N=16	40 / 20 mg OXN N=16	80 / 40 mg OXN N=16
Mean	6.9	9.1	6.0	8.6	12.5

Median	7.3	5.3	5.5	6.6	9.2
Minimum	0.0	0.0	0.0	0.0	0.0
Maximum	16.9	28.9	16.7	34.5	49.5

A general trend can be observed that with higher doses of naloxone administered there is a slight increase in the predicted values of maximum total SOWS at a low dose of oxycodone and a moderate increase at higher doses of oxycodone. It is noteworthy that the 2:1 ratio does not indicate additional safety concerns.

9. Laxative Intake/ Laxative Mean Dose Results

The mean number of days with laxative intake during the last 7 days prior to the end of maintenance decreased with increasing absolute dose of naloxone (3.9 ± 3.38, 2.6 ± 3.34, 2.0 ± 3.14, 1.6 ± 2,93 for placebo, 10 mg, 20 mg and 40 mg naloxone, respectively). The percentage of days (mean ± SD) with laxation during the entire maintenance phase showed a clear decrease for placebo with increasing dose of naloxone. The values being 46.4 ± 42.78, 36.5 ± 33.50, 31.3 ± 41.38 and 27.8 ± 41.25 for placebo, 10 mg, 20 mg and 40 mg naloxone. The mean number of days of laxative intake during the last 7 days prior to the end of maintenance was lowest at the 3/1 ratio and the 1.5/1 ratio. Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio shows no difference between the absolute dose of naloxone within either dose ratio group (4/1 and 2/1). The particulars can be taken from Figs. 14 and 15 and Table 7 below.

Table 7: Laxative Intake (days) by oxycodone/naloxone dose ratio (ITT population)

Visit Mean (S.D.)	40 mg Placebo N=17	60 mg Placebo N=17	80 mg Placebo N=16	40 / 20 mg OXN N=16	80 / 40 mg OXN N=16
Visit 3 - Randomization	4.5 (3.12)	4.8 (2.54)	4.6 (2.79)	4.8 (2.88)	5.5 (2.50)
Visit 4 - Maintenance 1w	1.8 (2.76)	2.3 (2.46)	2.3 (2.79)	2.1 (2.71)	1.6 (26.19)
Visit 5 - End maintenance	3.9 (3.30)	3.8 (3.55)	4.1 (3.52)	1.9 (3.20)	2.0 (3.22)

Visit 6 - End follow up	3.8 (3.63)	4.0 (3.09)	4.5 (3.35)	4.2 (3.38)	3.7 (3.53)

10. Adverse Events - Results

Figs. 16 to 19 provide an overall summary of adverse events during the maintenance phase by oxycodone/naloxone dose ratio and by absolute dose amount of naloxone. The number of patients experiencing any adverse events during the maintenance phase was comparable by absolute dose of naloxone and placebo (range 62.7% - 70%), although the number of events increased with increasing naloxone dose. No relationship to dose ratio could be identified. The incidence of adverse events during the follow-up phase was also comparable between oxycodone dose groups.

As regards severity of elicited opioid typical adverse events, the mean sum scores were generally low at ech study visit and during the maintenance phase for all treatment groups and dose ratios. During the maintenance phase there was a clear trend for a reduction in mean sum scores for all naloxone treatment groups and naloxone dose ratios when compared to placebo. At the end of the maintenance phase, the mean sum scores were lower in the naloxone treatment groups than in the placebo group with a statistically significant difference ($p<0.05$) for all naloxone treatment groups (see also Figure 20 and 21).

As regards severity of elicited naloxone typical adverse events, there was a trend towards increase mean sumscore with increasing dose of naloxone. However, mean sumscores for naloxone typical adverse events improved during the maintenance phase in allactive naloxone treatment groups and there were no statistically significant differences to placebo for any active naloxone treatment group at the end of the maintenance phase (see Figure 22 and 23).

This could indicate that during steady state elicited opioid typical adverse events are reduced while there is no increase for elicited naloxone typical adverse events if the inventive preparations are used.

11. Incidence of Diarrhea - Results

The number of subjects experiencing diarrhea that began during the maintenance phase was higher in the active naloxone treatment groups with the number of events increasing with higher doses. A trend was observed that with increasing doses of naloxone administered there is an increase in the absolute duration of diarrhea in subjects, who completed the clinical trial.

Nevertheless, comparatively favourable safety data can be detected for the 2:1 ratio of oxycodone and naloxone, whereas the 1.5:1 ratio seems to result in a higher incidence and longer duration of diarrhea.

Table 8 shows that the 2:1 ratio gave comparable results to the placebo.

Table 8: Comparison of days with diarrhea by treatment

Days of diarrhea	Grouping			
	OXY/Placebo	OXN 40/20	OXN 80/40	OXN total[1]
N	6 (12%)	5	5	10 (29%)
Mean	7.3	2.0	5.6	3.8
Median	5.5	1.0	2.0	2.0
Minimum	1.0	1.0	1.0	1.0
Maximum	20.0	5.0	22.0	22.0

[1] 2:1 ratio

The same can be observed with respect to the incidence of discontinuations from the study due to diarrhea (see Table 9).

Table 9: Incidence of Discontinuations due to Diarrhea

Total Daily Naloxone Dose (mg) \ Total Daily Oxycodone Dose (mg)	40	60	80
0	0/17 (0.0%)	0/17 (0.0%)	0/16 (0.0 %)
10	0/17 (0.0%)	0/12 (0.0%)	1/22 (4.5%)
20	1/17 (5.9%)	3/18 (16.7%)	0/16 (0.0%)
40	1/15 (6.7%)	3/18 (16.7%)	2/17 (11.8%)

12. Study Conclusions

While the study was not designed nor powered as a formal demonstration of non-inferiority of oxycodone/naloxone versus oxycodone/naloxone placebo, the administration of prolonged oxycodone and naloxone in combination was not associated descriptively with differences in the intensity of mean pain whether analyzed by dose ratios or absolute dose of naloxone.

The study demonstrated that addition of controlled release naloxone to controlled release oxycodone results in a statistically significant improvement in mean bowel function at the two higher doses of naloxone (20mg and 40mg). The improvement increases with decreasing oxycodone/naloxone ratio and appears to plateau at the 2:1 ratio, with the overall effect at 2:1 ratio approximately 50% greater than at 4:1. The data indicate that the bowel function improvement is in general a function of the ratio; i.e., the improvement is, in general, constant within each ratio, and independent of the varying doses of oxycodone and naloxone. The only exception is the 80/40 combination, where there is a suggestion of a lower predicted effect than for the 60/30 mg and 40/20 mg combinations.

The greatest improvements were seen at dose ratios of 1/1, 1.5/1 and 2/1 on absolute dose of 40 mg. Model estimates of oral treatment effect for specific ratios show minimal

improvement in bowel function between the 2/1 ratio and the 1.5/1 ratio, suggesting that the improvement in bowel function reaches a plateau at the 2/1 ratio.

A global assessment of efficacy and tolerability indicated an overall preference towards the 1/1 dose ratio for both investigators and patients. The 80 mg oxycodone/placebo, 8/1 and 2/1 dose ratios also had a high tolerability. The global assessment of preference also indicated that the majority of patients and investigators preferred the maintenance phase for the 1/1 dose ratio, but formed the 2/1 ratio also as suitable.

The incidence of naloxone- and opioid-typically adverse effects were summarized by sum scores for incidence and severity.

Most reported adverse events were those known to be associated with naloxone or oxycodone and diarrhea was the most frequently reported adverse event that increased with higher doses of naloxone. Diarrhea was the most common causally related adverse event and adverse event. The incidence of diarrhea was substantially reduced from the 1.5/1 to the 2/1 dose ratio. Diarrhea can be regarded as a typical withdrawal symptom for patients with opioid-induced constipation, who receive an opioid antagonist.

In summary, it seems that, if all aspects of treatment are taken into account, i.e. reduction of pain intensity, improvement of BFI, occurrence of adverse effect, avoidance of diarrhea and tolerability and preference, the 2/1 ratio seems to be the best choice. Within the 2/1 ratio, the 40/20 mg dose seems particularly suitable.

Figure 1: Patient Demographics and Other Baseline Characteristics by Absolute Dose of Naloxone

	Absolute Dose of Naloxone				
Characteristic	**Naloxone Placebo** N=50 (100%)	**Naloxone 10 mg** N=51 (100%)	**Naloxone 20 mg** N=51 (100%)	**Naloxone 40 mg** N=50 (100%)	**Total** N=202 (100%)
Sex n (%)					
Male	19 (38.0)	8 (35.3)	17 (33.3)	21 (42.0)	75 (37.1)
Female	31 (62.0)	33 (64.7)	34 (66.7)	29 (58.0)	127 (62.9)
Age [years]					
Mean	53.8	58.4	56.0	57.0	56.3
SD	12.74	12.75	12.65	14.03	13.06
Median	53.0	57.0	56.0	57.5	55.0
Min-Max	29 – 84	28 – 86	33 – 80	27 – 78	27 – 86
Race n (%)					
Caucasian	50 (100.0)	51 (100.0)	51 (100.0)	50 (100.0)	202 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)					
Mean	75.88	77.65	81.76	80.14	78.87
SD	13.43	14.47	13.92	18.11	15.14
Median	75.0	80.0	81.0	81.0	80.0
Min-Max	46 – 107	47 – 105	56 – 115	45 – 110	45 – 115
Height (cm)					
Mean	168.7	169.6	169.4	169.0	169.2
SD	8.29	8.00	7.97	9.12	8.30
Median	168.0	168.0	170.0	168.5	169.0
Min-Max	155 – 190	154 – 191	155 – 185	147 – 189	147 – 191
BMI (kg/m^2)					
Mean	26.70	27.03	28.65	27.93	27.58
SD	4.58	5.11	5.50	5.57	5.22
Median	26.03	25.83	27.78	28.09	26.61
Min-Max	17.1 – 40.3	17.3 – 37.2	18.9 – 42.6	16.8 – 39.8	16.8 – 42.6
Tumor patient n (%)					
Yes	1 (2.0)	1 (2.0)	1 (2.0)	2 (4.0)	5 (2.5)
No	49 (98.0)	50 (98.0)	50 (98.0)	48 (96.0)	197 (97.5)

Figure 2: Patient Demographics and Other Baseline Characteristics by Oxycodone/Naloxone Dose Ratio

	Dose Ratios									
	40 mg/ Placebo	**60 mg/ Placebo**	**80 mg/ Placebo**	**1/1**	**1.5/1**	**2/1**	**3/1**	**4/1**	**6/1**	**8/1**
Characteristic	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=18 (100%)	N=34 (100%)	N=18 (100%)	N=33 (100%)	N=12 (100%)	N=22 (100%)
Sex n (%)										
Male	6 (35.3)	6 (35.3)	7 (43.8)	5 (33.3)	8 (44.4)	11 (32.4)	8 (44.4)	10 (30.3)	4 (33.3)	10 (45.5)
Female	11 (64.7)	11 (64.7)	9 (56.3)	10 (66.7)	10 (55.6)	23 (67.6)	10 (55.6)	23 (69.7)	8 (66.7)	12 (54.5)
Age [years]										
Mean	51.8	52.8	56.9	59.9	55.9	56.1	58.3	57.6	57.6	55.9
SD	13.66	12.23	12.51	13.16	12.84	13.89	13.01	14.12	11.74	12.55
Median	52.0	53.0	56.5	61.0	55.5	60.0	60.5	52.0	61.0	55.0
Min-Max	37 – 84	29 – 75	31 – 80	34 – 78	35 – 72	27 – 76	39 – 80	35 – 86	34 – 73	28 - 77
Race n (%)										
Caucasian	17 (100.0)	17 (100.0)	16 (100.0)	15 (100.0)	18(100.0)	34 (100.0)	18 (100.0)	33 (100.0)	12 (100.0)	22 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)										
Mean	78.24	71.82	77.69	79.27	83.50	79.24	85.06	77.79	72.75	80.91
SD	11.00	15.33	13.45	17.71	20.36	15.78	11.93	14.34	14.23	14.26
Median	80.0	70.0	75.0	78.0	85.5	80.5	82.5	78.0	69.0	82.0
Min-Max	60 – 98	46 – 107	57 – 105	53 – 110	45 – 110	50 – 115	66 – 110	47 – 108	50 – 98	56 - 105
Height (cm)										
Mean	168.6	164.8	172.8	165.9	169.4	170.1	169.4	167.6	170.2	172.7
SD	6.56	6.52	9.87	8.62	8.87	7.80	9.19	7.98	9.29	7.22
Median	169.0	164.0	173.0	165.0	169.5	169.5	170.0	165.0	168.0	172.0
Min-Max	158 – 178	155 – 176	158 – 190	147 – 178	148 – 182	158 – 189	155 – 182	154 – 185	155 – 186	160- 191
BMI (kg/m^2)										
Mean	27.51	26.51	26.04	28.74	28.88	27.38	29.97	27.78	25.06	27.13
SD	3.64	5.77	4.18	5.94	5.96	5.19	5.83	5.41	4.36	4.73
Median	26.79	25.65	25.02	28.09	30.47	26.70	28.56	26.64	24.32	26.43
Min-Max	22.6–34.7	17.1–40.3	18.8–34.6	21.2–39.8	16.8–38.6	17.0–38.9	21.7–42.6	17.3–38.3	19.9–36.4	19.5–37.2
Tumor patient n (%)										
Yes	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.9)	1 (5.6)	1 (3.0)	0 (0.0)	0 (0.0)
No	16 (94.1)	17 (100.0)	16 (100.0)	15 (100.0)	17 (94.4)	33 (97.1)	17 (94.4)	32 (97.0)	12 (100.0)	22(100.0)

Figure 3

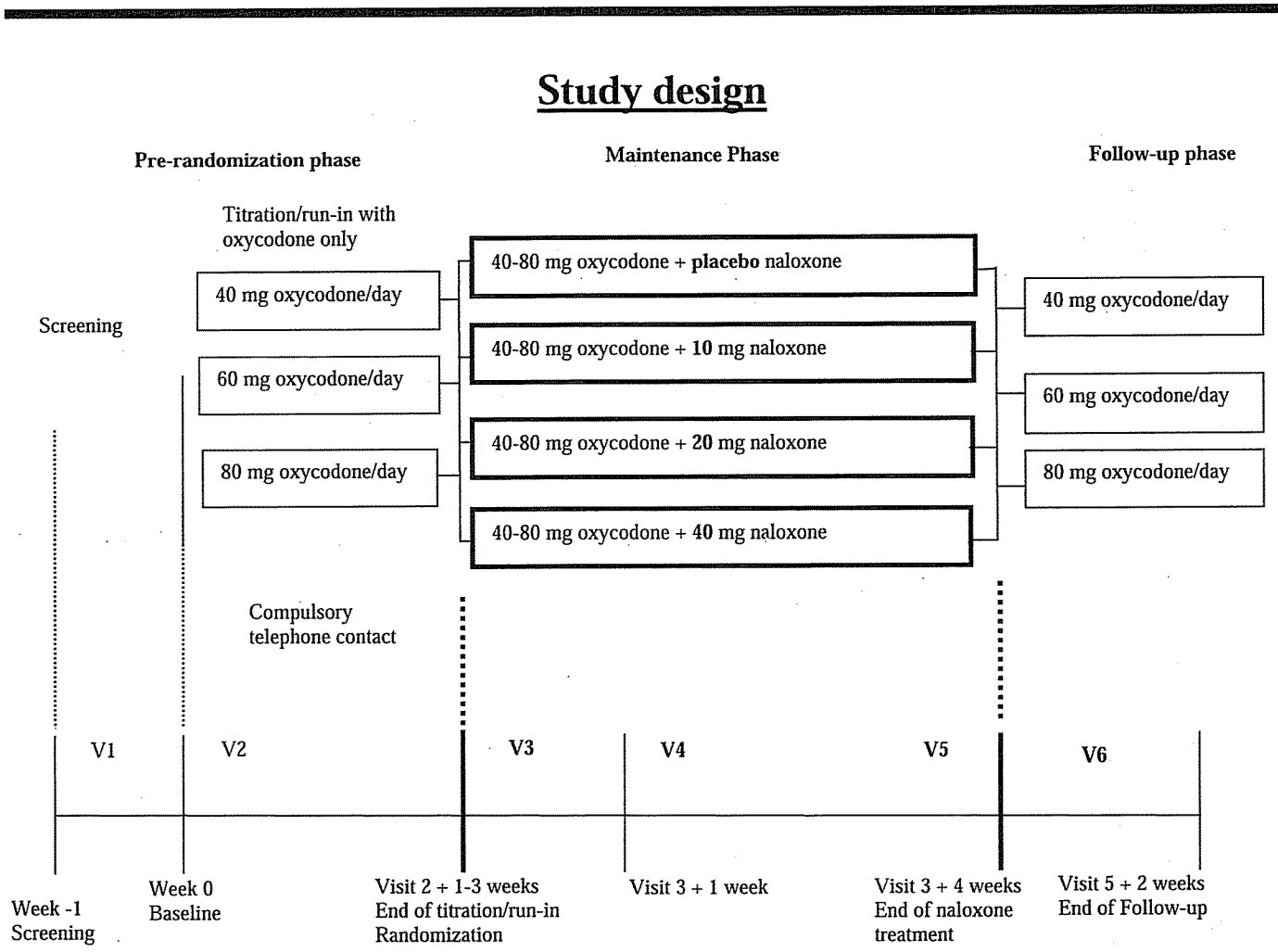

Study design
Pre-randomization phase
Maintenance Phase
Follow-up phase
Titration/run-in with oxycodone only
Screening
40 mg oxycodone/day
60 mg oxycodone/day
80 mg oxycodone/day
40-80 mg oxycodone + placebo naloxone
40-80 mg oxycodone + 10 mg naloxone
40-80 mg oxycodone + 20 mg naloxone
40-80 mg oxycodone + 40 mg naloxone
40 mg oxycodone/day
60 mg oxycodone/day
80 mg oxycodone/day
Compulsory telephone contact
V1
V2
V3
V4
V5
V6
Week -1 Screening
Week 0 Baseline
Visit 2 + 1-3 weeks End of titration/run-in Randomization
Visit 3 + 1 week
Visit 3 + 4 weeks End of naloxone treatment
Visit 5 + 2 weeks End of Follow-up

Figure 4:

Mean Bowel Function at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Average Bowel Function	**40 mg/ Placebo** N=17 (100%)	**60 mg/ Placebo** N=17 (100%)	**80 mg/ Placebo** N=16 (100%)	**1/1** N=15 (100%)	**1.5/1** N=15 (100%)	**2/1** N=32 (100%)	**3/1** N=17 (100%)	**4/1** N=32 (100%)	**6/1** N=11 (100%)	**8/1** N=22 (100%)
Visit 2 (Baseline)										
N	17	17	16	15	17	32	17	32	11	22
Mean	52.2	48.7	59.3	44.7	49.7	51.6	56.2	53.4	56.7	60.3
SD	21.66	28.79	17.93	15.42	18.20	21.54	19.20	22.57	19.94	18.51
Median	53.3	50.0	61.7	40.0	50.0	51.7	53.3	50.8	50.0	66.7
Min-Max	0-83	0-93	29-83	23-77	20-83	0-87	30-93	3-100	30-100	17-87
Visit 3 (Randomization)										
N	17	17	16	15	17	32	17	32	11	22
Mean	44.9	43.0	56.5	41.6	47.9	47.4	41.4	51.4	55.5	59.7
SD	25.77	26.35	17.70	20.03	21.90	20.19	21.28	23.36	23.86	22.16
Median	43.3	36.7	51.7	40.0	46.7	50.0	40.0	56.7	46.7	65.0
Min-Max	0-100	3-87	30-83	17-90	0-87	0-87	0-80	10-100	20-100	17-100
Visit 4 (Maintenance)										
N	15	17	16	15	14	28	16	31	11	21
Mean	41.4	48.3	39.6	20.7	22.3	35.4	25.2	41.6	44.8	45.7
SD	21.83	31.24	25.56	19.24	16.97	25.19	32.79	26.51	27.66	26.86
Median	43.3	50.0	45.0	20.0	20.0	33.3	11.7	40.0	43.3	40.0
Min-Max	0-87	0-93	0-73	0-53	0-53	0-77	0-100	0-100	0-80	0-100
Visit 5 (End of Maintenance)										
N	13	17	15	14	14	27	12	27	10	19
Mean	44.6	43.6	48.2	21.9	21.8	26.7	34.7	39.0	47.8	38.6
SD	22.42	23.75	21.71	22.25	21.35	23.98	26.99	26.24	23.20	24.68
Median	43.3	40.0	53.3	20.0	16.7	23.3	31.7	33.3	51.7	33.3
Min-Max	13-100	0-90	0-80	0-70	0-67	0-90	0-80	0-85	10-70	0-92
Visit 6 (End of Follow-up)										
N	13	17	15	14	13	26	12	28	10	18
Mean	52.1	47.4	48.2	33.2	47.3	42.6	43.9	51.0	49.3	42.9
SD	26.79	24.25	25.82	20.76	24.32	24.37	27.99	24.16	23.92	26.41
Median	50.0	50.0	50.0	35.0	46.7	43.3	41.7	50.0	50.0	45.0
Min-Max	7-100	0-90	0-90	0-80	0-80	0-80	0-90	0-100	10-80	0-80

Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

Figure 5:

Mean Bowel Function at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Average Bowel Function	**Naloxone Placebo** N=50 (100%)	**Naloxone 10 mg** N=49 (100%)	**Naloxone 20 mg** N=49 (100%)	**Naloxone 40 mg** N=48 (100%)
Visit 2 (Baseline)				
N	50	49	49	48
Mean	53.3	55.8	56.1	47.9
SD	23.28	19.81	20.19	19.65
Median	53.3	53.3	50.0	49.2
Min-Max	0-93	7-100	3-100	0-83
Visit 3 (Randomization)				
N	50	49	49	48
Mean	48.0	52.8	49.4	46.2
SD	23.97	22.86	22.72	20.67
Median	48.3	50.0	50.0	46.7
Min-Max	0-100	10-100	0-100	0-90
Visit 4 (Maintenance)				
N	48	47	47	42
Mean	43.3	42.1	34.2	27.9
SD	26.41	25.53	30.04	22.68
Median	46.7	40.0	30.0	28.3
Min-Max	0-93	0-100	0-100	0-73
Visit 5 (End of Maintenance)				
N	45	41	42	40
Mean	45.4	40.3	31.3	26.1
SD	22.28	23.09	25.82	25.08
Median	43.3	36.7	25.0	20.0
Min-Max	0-100	0-92	0-85	0-90
Visit 6 (End of Follow-up)				
N	45	41	41	39
Mean	49.0	45.1	46.4	42.4
SD	25.01	23.72	26.98	23.19
Median	50.0	50.0	43.3	40.0
Min-Max	0-100	0-80	0-100	0-80

Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

Figure 6:

Mean Bowel Function at Each Study Visit by Absolute Dose of Naloxone Given the Same Oxycodone/ Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose ratio			
Average Bowel Function	**4/1 10 mg naloxone** N=16 (100%)	**4/1 20 mg naloxone** N=16 (100%)	**2/1 20 mg naloxone** N=16 (100%)	**2/1 40 mg naloxone** N=16 (100%)
Visit 2 (Baseline)				
N	16	16	16	16
Mean	49.0	57.9	54.2	49.0
SD	20.76	24.06	18.04	24.88
Median	50.8	55.0	48.3	56.7
Min-Max	7-80	3-100	33-87	0-77
Visit 3 (Randomization)				
N	16	16	16	16
Mean	41.6	61.3	46.0	48.8
SD	19.90	22.73	20.44	20.51
Median	41.7	63.3	45.0	51.7
Min-Max	10-77	10-100	8-87	0-73
Visit 4 (Maintenance)				
N	15	16	15	13
Mean	35.0	47.8	29.3	42.3
SD	22.01	29.47	23.50	26.19
Median	40.0	43.3	30.0	46.7
Min-Max	0-72	0-100	0-77	0-73
Visit 5 (End of Maintenance)				
N	12	15	15	12
Mean	36.7	40.8	19.2	36.1
SD	20.74	30.54	13.58	30.84
Median	35.0	33.3	20.0	33.3
Min-Max	3-73	0-85	0-50	0-90
Visit 6 (End of Follow-up)				
N	13	15	14	12
Mean	45.0	56.2	38.1	47.8
SD	20.86	26.27	25.34	23.15
Median	50.0	50.0	36.7	55.0
Min-Max	0-70	23-100	0-80	0-77

Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

Figure 7:

Mean Bowel Function: Test for Difference Versus Placebo - ITT Population with Non-missing Values

	Absolute Dose of Naloxone		
Category	**Naloxone 10 mg vs Placebo**	**Naloxone 20 mg vs Placebo**	**Naloxone 40 mg vs Placebo**
Mean bowel function assessing the last 7 days at Visit 4			
N in test group	47	47	42
N in placebo group	48	48	48
Difference in means*	-1.2	-9.0	-15.4
95% CI	(-11.8, 9.4)	(-20.6, 2.5)	(-25.8, -5.0)
P-value**	0.827	0.122	0.004
Mean bowel function assessing the last 7 days at Visit 5 (end of maintenance)			
N in test group	41	42	40
N in placebo group	45	45	45
Difference in means*	-5.1	-14.1	-19.3
95% CI	(-14.9, 4.6)	(-24.4, -3.8)	(-29.5, -9.1)
P-value**	0.296	0.008	<0.001

*Mean in test group minus mean in placebo group; **t-test for difference

Figure 8:

Mean Bowel Function: Response Surface Plot - ITT Population with Non-missing Values

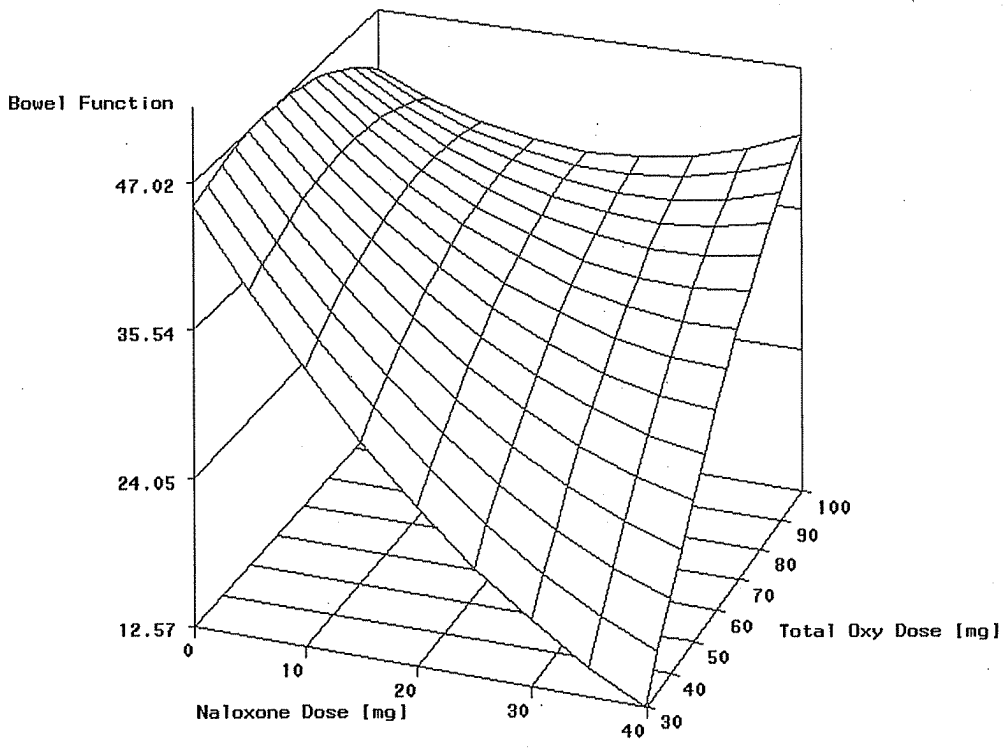
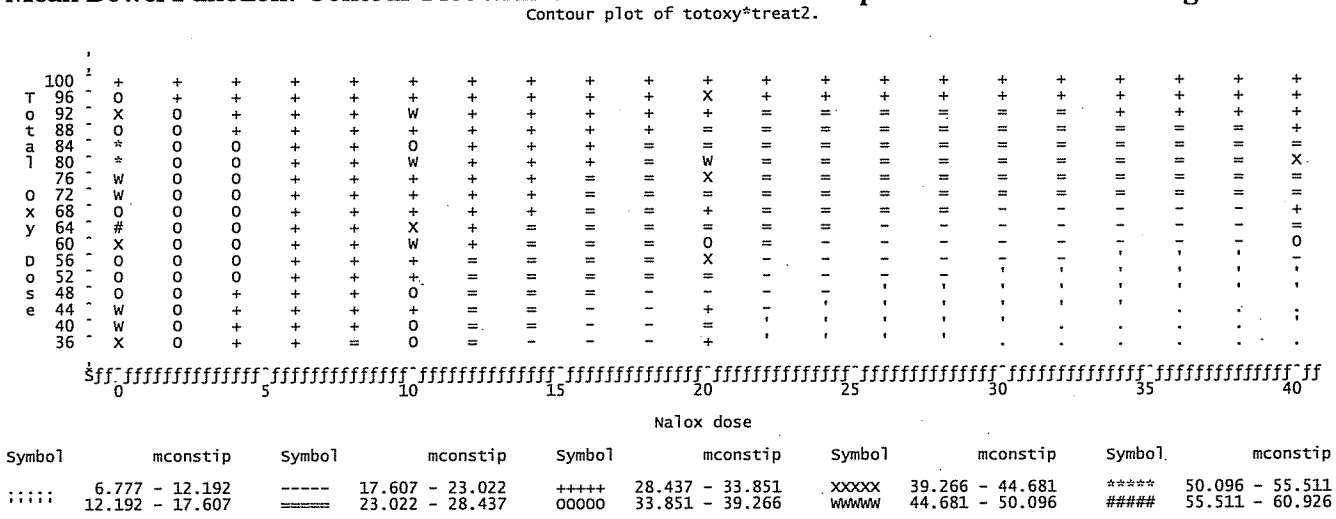


Figure 9:

Mean Bowel Function: Contour Plot with Granulation 10 - ITT Population with Non-missing Values



NOTE: 484 obs hidden. 1 obs out of range.

Fig. 10 **Global Assessment by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values**

Assessment at end of maintenance phase (n, (%))	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	Dose Ratios 1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Efficacy (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	2 (11.8)	2 (11.8)	2 (12.5)	2 (13.3)	3 (17.6)	4 (12.5)	2 (11.8)	5 (15.6)	0 (0.0)	2 (9.1)
Good	8 (47.1)	5 (29.4)	3 (18.8)	9 (60.0)	6 (35.3)	15 (46.9)	8 (47.1)	13 (40.6)	4 (36.4)	7 (31.8)
Fairly good	1 (5.9)	3 (17.6)	3 (18.8)	2 (13.3)	1 (5.9)	5 (15.6)	0 (0.0)	2 (6.3)	1 (9.1)	3 (13.6)
Moderate	1 (5.9)	2 (11.8)	3 (18.8)	1 (6.7)	2 (11.8)	1 (3.1)	1 (5.9)	3 (9.4)	5 (45.5)	4(18.2)
Slightly poor	1 (5.9)	3 (17.6)	1 (6.3)	0 (0.0)	1 (5.9)	1(3.1)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Poor	0 (0.0)	1 (5.9)	2 (12.5)	0 (0.0)	0 (0.0)	1 (3.1)	1(5.9)	5 (15.6)	0 (0.0)	2 (9.1)
Very poor	1 (5.9)	1 (5.9)	1 (6.3)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Efficacy (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	1 (5.9)	1 (5.9)	2 (12.5)	2 (13.3)	4 (23.5)	6 (18.8)	2 (11.8)	3 (9.4)	0 (0.0)	1 (4.5)
Good	7 (41.2)	7 (41.2)	2 (12.5)	8 (53.3)	7 (41.2)	13 (40.6)	9 (52.9)	14 (43.8)	3 (27.3)	7 (31.8)
Fairly good	1 (5.9)	2 (11.8)	3 (18.8)	3 (20.0)	0 (0.0)	3 (9.4)	0 (0.0)	4 (12.5)	2 (18.2)	1 (4.5)
Moderate	3 (17.6)	2 (11.8)	4 (25.0)	1 (6.7)	2 (11.8)	3 (9.4)	1 (5.9)	2 (6.3)	4 (36.4)	5 (22.7)
Slightly poor	0 (0.0)	3 (17.6)	1 (6.3)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	2 (6.3)	1 (9.1)	3 (13.6)
Poor	1 (5.9)	0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	4 (12.5)	0 (0.0)	2 (9.1)
Very poor	1 (5.9)	2 (11.8)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	2 (11.8)	5 (29.4)	2 (12.5)	3 (20.0)	4 (23.5)	9 (28.1)	4 (23.5)	5 (15.6)	1 (9.1)	5 (22.7)
Good	10 (58.8)	6 (35.3)	11 (68.8)	10 (66.7)	7 (41.2)	13 (40.6)	7 (41.2)	17 (53.1)	6 (54.5)	12 (54.5)
Fairly good	1 (5.9)	1 (5.9)	2 (12.5)	1 (6.7)	2 (11.8)	5 (15.6)	1 (5.9)	4 (12.5)	3 (27.3)	0 (0.0)
Moderate	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Slightly poor	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Poor	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)
Very poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	1 (5.9)	4 (23.5)	2 (12.5)	2 (13.3)	3 (17.6)	7 (21.9)	3 (17.6)	5 (15.6)	1 (9.1)	5 (22.7)
Good	10 (58.8)	7 (41.2)	9 (56.3)	10 (66.7)	8 (47.1)	15 (46.9)	8 (47.1)	17 (53.1)	6 (54.5)	12 (54.5)
Fairly good	1 (5.9)	2 (11.8)	2 (12.5)	2 (13.3)	1 (5.9)	3 (9.4)	1 (5.9)	3 (9.4)	3 (27.3)	0 (0.0)
Moderate	1 (5.9)	1 (5.9)	2 (12.5)	0 (0.0)	2 (11.8)	2 (6.3)	0 (0.0)	2 (6.3)	0 (0.0)	1 (4.5)
Slightly poor	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Poor	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very poor	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)

Fig. 10 continued

Global Assessment by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

Assessment at end of maintenance phase (n, (%))	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Preference regarding efficacy (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	7 (41.2)	6 (37.5)	2 (13.3)	5 (29.4)	4 (12.5)	5 (29.4)	10 (31.3)	1 (9.1)	8 (36.4)
Maintenance phase	5 (29.4)	5 (29.4)	4 (25.0)	10 (66.7)	7 (41.2)	13 (40.6)	5 (29.4)	12 (37.5)	4 (36.4)	7 (31.8)
No preference	5 (29.4)	5 (29.4)	5 (31.3)	2 (13.3)	2 (11.8)	10 (31.3)	2 (11.8)	7 (21.9)	5 (45.5)	4 (18.2)
Preference regarding efficacy (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	8 (47.1)	5 (31.3)	1 (6.7)	5 (29.4)	4 (12.5)	5 (29.4)	9 (28.1)	1 (9.1)	9 (40.9)
Maintenance phase	6 (35.3)	5 (29.4)	5 (31.3)	10 (66.7)	7 (41.2)	14 (43.8)	6 (35.3)	13 (40.6)	4 (36.4)	7 (31.8)
No preference	4 (23.5)	4 (23.5)	5 (31.3)	3 (20.0)	2 (11.8)	9 (28.1)	1 (5.9)	7 (21.9)	5 (45.5)	3 (13.6)
Preference regarding tolerability (investigator)										
N	14 (82.4)	17 (100)	16 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	7 (41.2)	4 (25.0)	0 (0.0)	5 (29.4)	4 (12.5)	2 (11.8)	9 (28.1)	1 (9.1)	5 (22.7)
Maintenance phase	5 (29.4)	5 (29.4)	6 (37.5)	12 (80.0)	7 (41.2)	15 (46.9)	8 (47.1)	13 (40.6)	5 (45.5)	10 (45.5)
No preference	5 (29.4)	5 (29.4)	5 (31.3)	2 (13.3)	2 (11.8)	8 (25.0)	2 (11.8)	7 (21.9)	4 (36.4)	4 (18.2)
Preference regarding tolerability (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	7 (41.2)	4 (25.0)	0 (0.0)	5 (29.4)	4 (12.5)	2 (11.8)	8 (25.0)	1 (9.1)	5 (22.7)
Maintenance phase	5 (29.4)	5 (29.4)	6 (37.5)	11 (73.3)	7 (41.2)	15 (46.9)	9 (52.9)	15 (46.9)	5 (45.5)	10 (45.5)
No preference	5 (29.4)	5 (29.4)	5 (31.3)	3 (20.0)	2 (11.8)	8 (25.0)	1 (5.9)	6 (18.8)	4 (36.4)	4 (18.2)

Fig. 11 Global Assessment by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Assessment at end of maintenance phase (n, (%))	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Efficacy (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	6 (12.0)	5 (10.2)	6 (12.2)	7 (14.6)
Good	16 (32.0)	18 (36.7)	23 (46.9)	21 (43.8)
Fairly good	7 (14.0)	6 (12.2)	3 (6.1)	5 (10.4)
Moderate	6 (12.0)	10 (20.4)	4 (8.2)	3 (6.3)
Slightly poor	5 (10.0)	1 (2.0)	1 (2.0)	2 (4.2)
Poor	3 (6.0)	2 (4.1)	6 (12.2)	1 (2.1)
very poor	3 (6.0)	0 (0.0)	0 (0.0)	1 (2.1)
Efficacy (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	4 (8.0)	3 (6.1)	5 (10.2)	10 (20.8)
Good	16 (32.0)	18 (36.7)	24 (49.0)	19 (39.6)
Fairly good	6 (12.0)	5 (10.2)	4 (8.2)	4 (8.3)
Moderate	9 (18.0)	10 (20.4)	4 (8.2)	4 (8.3)
Slightly poor	4 (8.0)	4 (8.2)	2 (4.1)	1 (2.1)
Poor	4 (8.0)	2 (4.1)	4 (8.2)	1 (2.1)
very poor	3 (6.0)	0 (0.0)	0 (0.0)	1 (2.1)
Tolerability (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	9 (18.0)	8 (16.3)	13 (26.5)	10 (20.8)
Good	27 (54.0)	27 (55.1)	21 (42.9)	24 (50.0)
Fairly good	4 (8.0)	5 (10.2)	6 (12.2)	5 (10.4)
Moderate	2 (4.0)	1 (2.0)	1 (2.0)	1 (2.1)
Slightly poor	3 (6.0)	1 (2.0)	0 (0.0)	0 (0.0)
Poor	1 (2.0)	0 (0.0)	2 (4.1)	0 (0.0)
very poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	7 (14.0)	9 (18.4)	9 (18.4)	8 (16.7)
Good	26 (52.0)	26 (53.1)	25 (51.0)	25 (52.1)
Fairly good	5 (10.0)	5 (10.2)	3 (6.1)	5 (10.4)
Moderate	4 (8.0)	1 (2.0)	4 (8.2)	2 (4.2)
Slightly poor	2 (4.0)	1 (2.0)	1 (2.0)	0 (0.0)
Poor	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
very poor	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)

Fig. 11 continued

Global Assessment by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Assessment at end of maintenance phase (n, (%))	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Preference regarding efficacy (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	17 (34.0)	11 (22.4)	15 (30.6)	9 (18.8)
Maintenance phase	14 (28.0)	19 (38.8)	16 (32.7)	23 (47.9)
No preference	15 (30.0)	12 (24.5)	12 (24.5)	8 (16.7)
Preference regarding efficacy (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	17 (34.0)	12 (24.5)	14 (28.6)	8 (16.7)
Maintenance phase	16 (32.0)	19 (38.8)	19 (38.8)	23 (47.9)
No preference	13 (26.0)	11 (22.4)	10 (20.4)	9 (18.8)
Preference regarding tolerability (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	15 (30.0)	8 (16.3)	10 (20.4)	8 (16.7)
Maintenance phase	16 (32.0)	22 (44.9)	24 (49.0)	24 (50.0)
No preference	15 (30.0)	12 (24.5)	9 (18.4)	8 (16.7)
Preference regarding tolerability (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	15 (30.0)	8 (16.3)	9 (18.4)	8 (16.7)
Maintenance phase	16 (32.0)	23 (46.9)	26 (53.1)	23 (47.9)
No preference	15 (30.0)	11 (22.4)	8 (16.3)	9 (18.8)

Figure 12

Global assessment – efficacy patients,
relative frequencies by absolute naloxone dose (ITT)

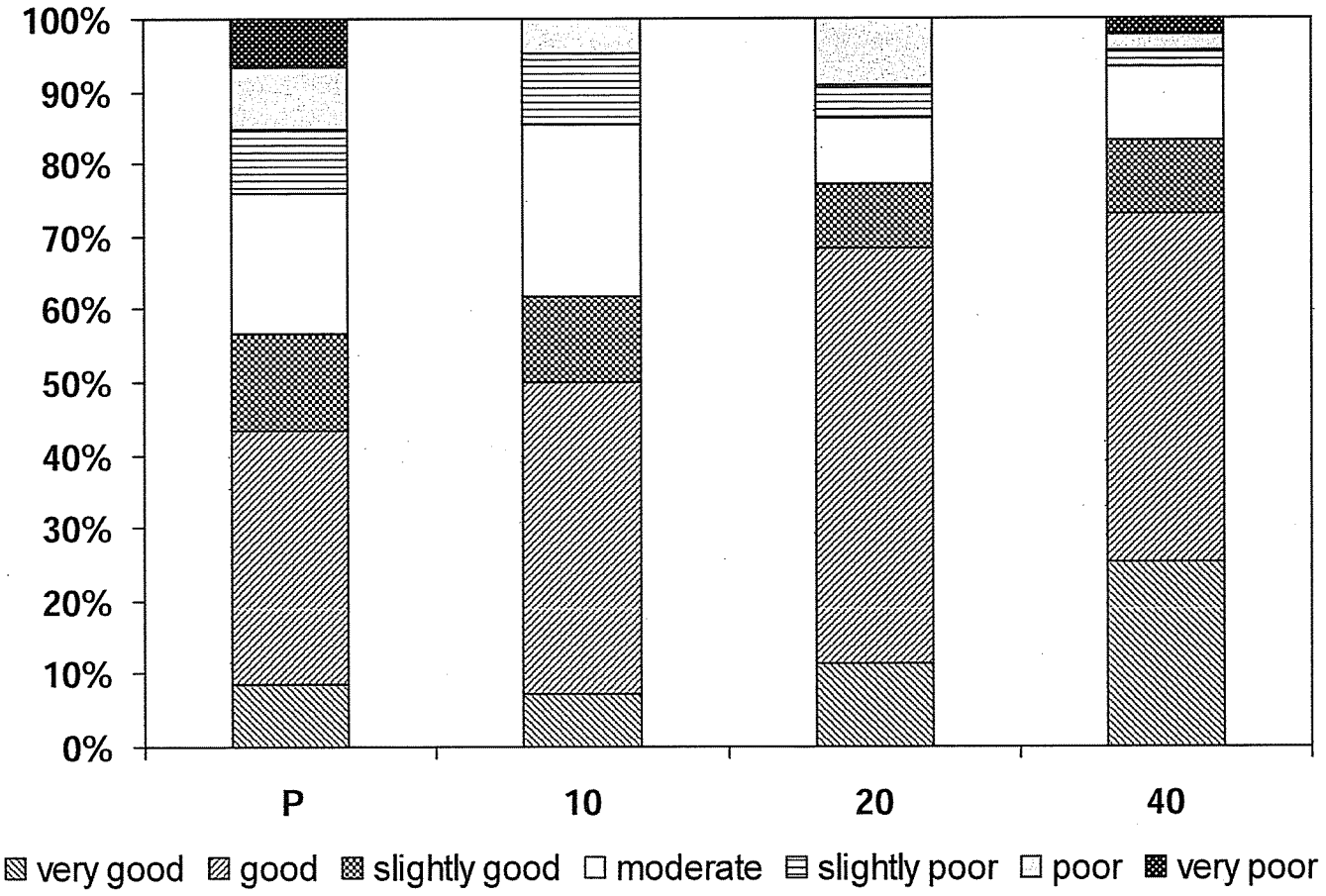


Figure 13

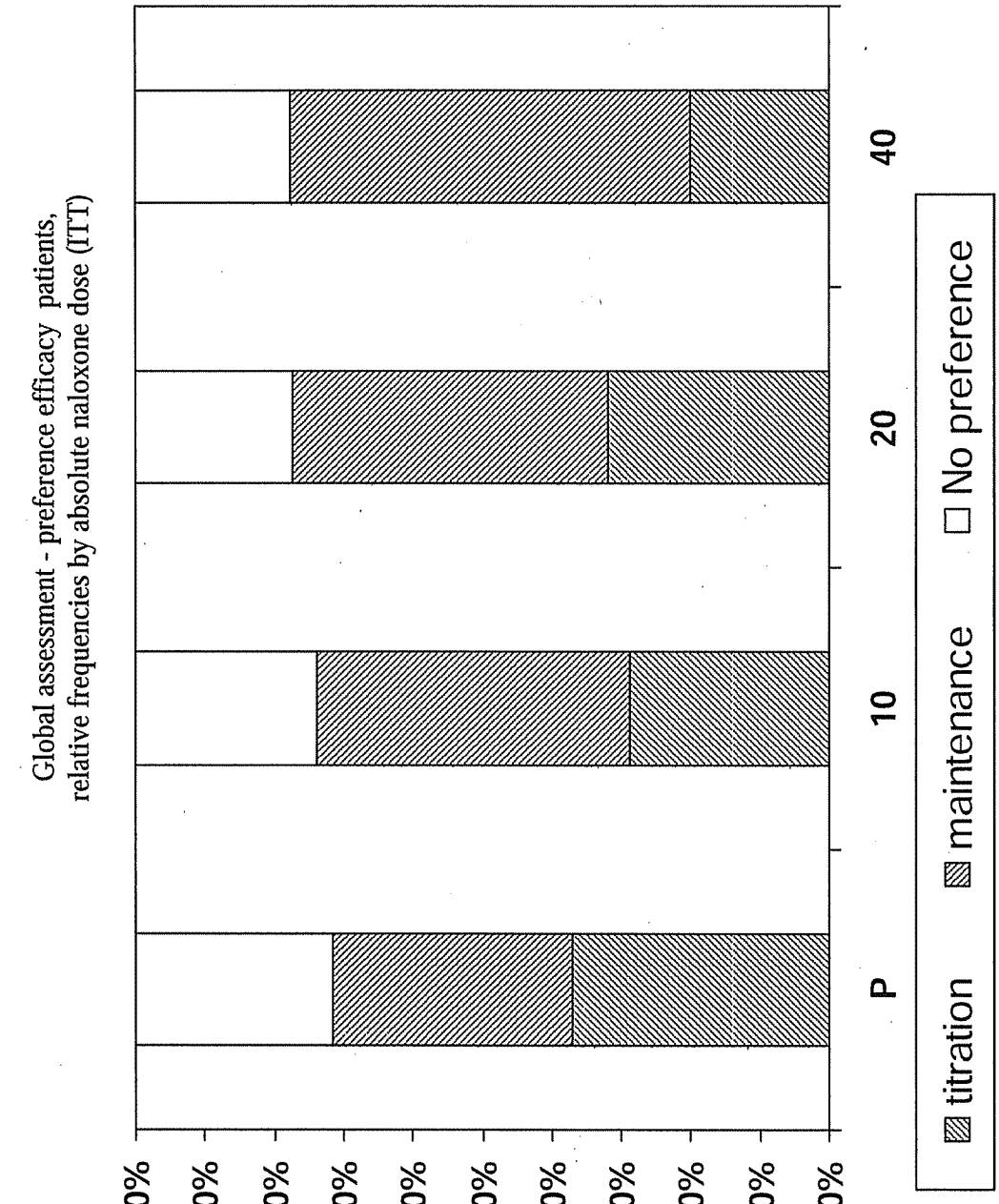

Global assessment - preference efficacy patients,
relative frequencies by absolute naloxone dose (ITT)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
P
10
20
40
titration
maintenance
No preference

Fig. 14 Laxative Intake at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing

Number of days with Laxative Intake	Dose Ratios									
	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 3 (Randomization)*										
N (n†)	17 (15)	15 (16)	14 (14)	12 (14)	16 (16)	31 (31)	16 (15)	29 (30)	8 (11)	20 (19)
Mean	4.5	4.8	4.6	5.3	5.0	5.2	4.7	4.8	6.3	4.1
SD	3.12	2.54	2.79	2.99	2.88	2.68	2.85	3.10	1.75	3.21
Median	6.0	6.0	6.0	7.0	7.0	7.0	6.0	7.0	7.0	5.5
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	2-7	0-7
Visit 4 (Maintenance)*										
N (n†)	15 (8)	16 (13)	15 (10)	15 (9)	14 (6)	26 (16)	16 (4)	31 (21)	9 (9)	20 (12)
Mean	1.8	2.3	2.3	2.3	1.3	1.9	1.0	2.6	3.2	1.3
SD	2.76	2.46	2.79	2.71	2.05	2.58	2.07	2.74	2.39	1.89
Median	0.0	1.0	1.0	1.0	0.0	0.0	0.0	2.0	4.0	0.5
Min-Max	0-7	0-6	0-7	0-7	0-6	0-7	0-6	0-7	0-6	0-6
Visit 5 (End of Maintenance)*										
N (n†)	14 (10)	15 (13)	14 (12)	12 (8)	13 (5)	26 (13)	10 (4)	26 (17)	7 (8)	19 (10)
Mean	3.9	3.8	4.1	1.8	1.2	1.9	1.0	3.3	3.1	1.7
SD	3.30	3.55	3.52	3.17	2.61	3.15	2.31	3.53	3.63	2.94
Median	5.0	7.0	7.0	0.0	0.0	0.0	0.0	0.5	1.0	0.0
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7
Visit 6 (End of Follow-up)*										
N (n†)	13 (10)	15 (14)	14 (13)	12 (11)	11 (11)	24 (21)	11 (8)	24 (19)	6 (6)	13 (14)
Mean	3.8	4.0	4.5	2.8	3.4	4.0	2.3	4.1	3.5	3.9
SD	3.63	3.09	3.35	3.38	3.50	3.38	3.10	3.53	3.83	3.50
Median	7.0	5.0	7.0	0.5	1.0	7.0	1.0	7.0	3.5	7.0
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7
Entire Maintenance Phase**										
N (n†)	15 (12)	16 (15)	16 (14)	15 (10)	15 (9)	26 (24)	16 (9)	32 (25)	9 (9)	21 (17)
Mean	42.9	44.8	51.2	33.4	21.7	31.1	20.4	43.8	44.2	25.1
SD	44.60	43.84	42.37	42.87	39.71	41.47	39.80	42.57	43.13	33.54
Median	25.0	31.3	60.7	15.8	0.0	7.0	0.0	24.6	39.3	7.7
Min-Max	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100

*Number of days with laxation intake during the last 7 days according to patient diary; **Percentage of days with laxation intake during the maintenance phase according to patient diary n† Number of patients taking laxatives

Fig. 15 Laxative Intake at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Number of days with Laxative Intake	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N (n†)	46 (45)	44 (44)	45 (47)	43 (45)
Mean	4.6	4.7	4.8	5.3
SD	2.78	2.99	2.91	2.73
Median	6.0	7.0	7.0	7.0
Min-Max	0-7	0-7	0-7	0-7
Visit 4 (Maintenance)*				
N (n†)	46 (31)	44 (31)	47 (24)	40 (22)
Mean	2.1	2.2	1.8	1.8
SD	2.62	2.46	2.52	2.42
Median	1.0	1.0	0.0	0.0
Min-Max	0-7	0-7	0-7	0-7
Visit 5 (End of Maintenance)*				
N (n†)	43 (35)	37 (26)	40 (18)	36 (21)
Mean	3.9	2.6	2.0	1.6
SD	3.38	3.34	3.14	2.93
Median	7.0	0.0	0.0	0.0
Min-Max	0-7	0-7	0-7	0-7
Visit 6 (End of Follow-up)*				
N (n†)	42 (37)	32 (29)	36 (31)	33 (32)
Mean	4.1	3.6	3.9	3.3
SD	3.28	3.51	3.37	3.38
Median	6.5	4.5	7.0	1.0
Min-Max	0-7	0-7	0-7	0-7
Entire Maintenance Phase**				
N (n†)	47 (41)	46 (38)	47 (35)	41 (30)
Mean	46.4	36.5	31.3	27.8
SD	42.78	39.50	41.38	41.25
Median	37.5	15.8	7.1	3.6
Min-Max	0-100	0-100	0-100	0-100

*Number of days with laxation intake during the last 7 days according to patient diary; **Percentage of days with laxation intake during the maintenance phase according to patient diary n† Number of patients taking laxatives

Figure 16 **Overall Summary of Adverse Events During the Maintenance Phase by Oxycodone/Naloxone Dose Ratio - Safety Population**

Category	Dose Ratios																			
	40 mg/ Placebo		60 mg/ Placebo		80 mg/ Placebo		1/1		1.5/1		2/1		3/1		4/1		6/1		8/1	
	N=17 (100%)		N=17 (100%)		N=16 (100%)		N=15 (100%)		N=18 (100%)		N=84 (100%)		N=18 (100%)		N=33 (100%)		N=12 (100%)		N=22 (100%)	
	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)
Adverse Events	21	8 (47.1)	54	15 (88.2)	36	9 (56.3)	26	8 (53.3)	61	16 (88.9)	84	19 (55.9)	57	11 (61.1)	73	22 (66.7)	18	9 (75.0)	69	17 (77.3)
Causally Related#	12	6 (35.3)	33	11 (64.7)	29	8 (50.0)	23	7 (46.7)	44	12 (66.7)	70	19 (55.9)	40	8 (44.4)	60	18 (54.5)	14	6 (50.0)	51	13 (59.1)
Leading to discontinuation of study drug	0	0 (0.0)	0	0 (0.0)	1	1 (6.3)	3	1 (6.7)	14	4 (22.2)	15	5 (14.7)	27	5 (27.8)	2	2 (6.1)	1	1 (8.3)	10	2 (9.1)
Serious Adverse Events	0	0 (0.0)	0	0 (0.0)	1	1 (6.3)	0	0 (0.0)	2	2 (11.1)	1	1 (2.9)	1	1 (5.6)	1	1 (3.0)	1	1 (8.3)	3	1 (4.5)
Causally Related#	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (5.6)	1	1 (2.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	3	1 (4.5)
Leading to discontinuation of study drug	0	0 (0.0)	0	0 (0.0)	1	1 (6.3)	0	0 (0.0)	2	2 (11.1)	1	1 (2.9)	1	1 (5.6)	1	1 (3.0)	1	1 (8.3)	3	1 (4.5)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

E = Number of events

= Related adverse events include all events listed with a definite, probable, possible or unknown/missing relationship to study drug

Figure 17 **Overall Summary of Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone - Safety Population**

	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
Category	E	N (%)	E	N (%)	E	N (%)	E	N (%)
Adverse Events	111	32 (64.0)	119	35 (68.6)	129	32 (62.7)	140	35 (70.0)
Causally Related#	74	25 (50.0)	93	26 (51.0)	100	27 (52.9)	109	30 (60.0)
Leading to discontinuation of study drug	1	1 (2.0)	13	5 (9.8)	29	6 (11.8)	30	9 (18.0)
Serious Adverse Events	1	1 (2.0)	5	3 (5.9)	1	1 (2.0)	3	3 (6.0)
Causally Related#	0	0 (0.0)	3	1 (2.0)	0	0 (0.0)	2	2 (4.0)
Leading to discontinuation of study drug	1	1 (2.0)	5	3 (5.9)	1	1 (2.0)	3	3 (6.0)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

E = Number of events
# = Related adverse events include all events listed with a definite, probable, possible or unknown/missing relationship to study drug

Fig. 18 Adverse Events During the Maintenance Phase by Oxycodone/Naloxone Dose Ratio (Reported by ≥ 20% of Patients) and System Organ Class - Safety Population

System Organ Class	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=18 (100%)	N=34 (100%)	N=18 (100%)	N=33 (100%)	N=12 (100%)	N=22 (100%)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gastrointestinal Disorders	5 (29.4)	10 (58.8)	4 (25.0)	7 (46.7)	11 (61.1)	16 (47.1)	8 (44.4)	16 (48.5)	6 (50.0)	9 (40.9)
Skin and Subcutaneous Tissue Disorders	4 (23.5)	6 (35.3)	6 (37.5)	4 (26.7)	8 (44.4)	8 (23.5)	8 (44.4)	9 (27.3)	1 (8.3)	11 (50.0)
Nervous System Disorders	3 (17.6)	8 (47.1)	6 (37.5)	1 (6.7)	8 (44.4)	9 (26.5)	5 (27.8)	5 (15.2)	1 (8.3)	5 (22.7)
Musculoskeletal and Connective Tissue Disorders	3 (17.6)	3 (17.6)	1 (6.3)	3 (20.0)	3 (16.7)	7 (20.6)	4 (22.2)	9 (27.3)	2 (16.7)	5 (22.7)
Psychiatric Disorders	3 (17.6)	5 (29.4)	3 (18.8)	2 (13.3)	4 (22.2)	6 (17.6)	4 (22.2)	6 (18.2)	2 (16.7)	5 (22.7)
Ear and Labyrinth Disorders	0 (0.0)	6 (35.3)	2 (12.5)	1 (6.7)	3 (16.7)	4 (11.8)	2 (11.1)	2 (6.1)	1 (8.3)	3 (13.6)

Fig. 19

Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone (Reported by ≥ 10% of Patients) and System Organ Class - Safety Population

System Organ Class	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
	N	(%)	N	(%)	N	(%)	N	(%)
Gastrointestinal Disorders	19	(38.0)	22	(43.1)	24	(47.1)	27	(54.0)
Skin and Subcutaneous Tissue Disorders	16	(32.0)	17	(33.3)	16	(31.4)	16	(32.0)
Nervous System Disorders	17	(34.0)	9	(17.6)	11	(21.6)	14	(28.0)
Musculoskeletal and Connective Tissue Disorders	7	(14.0)	8	(15.7)	13	(25.5)	12	(24.0)
Psychiatric Disorders	11	(22.0)	10	(19.6)	8	(15.7)	11	(22.0)
Ear and Labyrinth Disorders	8	(16.0)	6	(11.8)	4	(7.8)	6	(12.0)
General disorders and administration site conditions	0	(0.0)	5	(9.8)	4	(7.8)	5	(10.0)

Fig. 20 **Sumscores for Elicited Naloxone Typical Adverse events at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values**

	Dose Ratios									
Sumscores	**40 mg/ Placebo** N=17 (100%)	**60 mg/ Placebo** N=17 (100%)	**80 mg/ Placebo** N=16 (100%)	**1/1** N=15 (100%)	**1.5/1** N=17 (100%)	**2/1** N=32 (100%)	**3/1** N=17 (100%)	**4/1** N=32 (100%)	**6/1** N=11 (100%)	**8/1** N=22 (100%)
Visit 4 (Maintenance)*										
N ($n^{\dagger}$)	15 (1)	17 (5)	16 (0)	15 (3)	15 (6)	28 (6)	16 (5)	31 (8)	11 (2)	21 (2)
Mean	0.1	0.4	0.0	0.7	1.1	0.7	0.8	0.6	0.4	0.4
SD	0.26	0.71	0.0	1.71	2.12	1.44	1.47	1.38	0.81	1.43
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-2	0-0	0-6	0-8	0-4	0-4	0-6	0-2	0-6
Visit 5 (End of Maintenance)*										
N ($n^{\dagger}$)	14 (1)	17 (4)	15 (1)	14 (0)	14 (4)	28 (4)	12 (0)	29 (3)	10 (1)	19 (1)
Mean	0.1	0.3	0.1	0.0	0.4	0.4	0.0	0.1	0.2	0.1
SD	0.27	0.59	0.26	0.0	0.85	0.99	0.0	0.31	0.63	0.23
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-2	0-1	0-0	0-3	0-4	0-0	0-1	0-2	0-1
Entire Maintenance Phase**										
N ($n^{\dagger}$)	15 (3)	17 (9)	16 (3)	15 (5)	15 (9)	29 (10)	16 (6)	31 (12)	11 (4)	21 (9)
Mean	0.4	0.9	0.3	1.1	1.5	1.2	1.1	1.3	0.8	1.0
SD	1.06	1.11	0.58	1.96	2.20	1.93	1.81	1.88	1.33	1.66
Median	0.0	1.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-4	0-4	0-2	0-6	0-8	0-6	0-6	0-6	0-4	0-7

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
$n^{\dagger}$ Number of patients with at least one elicited naloxone typical side effect

Fig. 21 **Sumscores for Elicited Naloxone Typical Adverse events at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values**

	Absolute Dose of Naloxone			
Sumscores	**Naloxone Placebo** N=50 (100%)	**Naloxone 10 mg** N=49 (100%)	**Naloxone 20 mg** N=49 (100%)	**Naloxone 40 mg** N=48 (100%)
Visit 4 (Maintenance)*				
N (n†)	48 (6)	47 (6)	47 (14)	43 (12)
Mean	0.2	0.3	0.8	0.9
SD	0.48	1.07	1.47	1.84
Median	0.0	0.0	0.0	0.0
Min-Max	0-2	0-6	0-6	0-8
Visit 5 (End of Maintenance)*				
N (n†)	46 (6)	42 (4)	43 (4)	41 (5)
Mean	0.2	0.1	0.2	0.2
SD	0.42	0.40	0.57	0.80
Median	0.0	0.0	0.0	0.0
Min-Max	0-2	0-2	0-3	0-4
Entire Maintenance Phase**				
N (n†)	48 (15)	47 (17)	47 (18)	44 (20)
Mean	0.5	0.8	1.2	1.4
SD	0.97	1.43	1.94	2.06
Median	0.0	0.0	0.0	0.0
Min-Max	0-4	0-7	0-6	0-8

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited naloxone typical side effect

Fig. 22 **Sumscores for Elicited Opioid Typical Adverse events at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values**

Sumscores	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Visit 3 (Randomization)*										
N (n†)	17 (2)	17 (5)	16 (3)	15 (3)	17 (6)	32 (3)	17 (10)	32 (10)	11 (1)	22 (8)
Mean	0.4	1.0	0.4	0.2	0.7	0.3	1.5	1.0	0.5	0.9
SD	1.22	1.77	1.02	0.41	1.10	0.95	1.66	1.82	1.51	1.36
Median	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-4	0-1	0-3	0-5	0-5	0-7	0-5	0-4
Visit 4 (Maintenance)*										
N (n†)	15 (4)	17 (10)	16 (4)	15 (5)	15 (7)	28 (6)	16 (8)	31 (10)	11 (1)	21(10)
Mean	0.7	1.0	0.5	0.5	1.7	0.5	1.4	0.6	0.4	0.9
SD	1.40	1.27	1.03	0.83	2.96	1.29	2.22	1.09	1.21	1.18
Median	0.0	1.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0
Min-Max	0-5	0-5	0-3	0-2	0-10	0-5	0-8	0-5	0-4	0-4
Visit 5 (End of Maintenance)*										
N (n†)	14 (2)	17 (7)	15 (2)	14 (0)	14 (2)	28 (0)	12 (1)	29 (4)	10 (1)	19(4)
Mean	0.6	1.1	0.3	0.0	0.3	0.0	0.1	0.3	0.2	0.3
SD	1.50	1.56	0.70	0.0	0.83	0.0	0.29	0.75	0.63	0.56
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-2	0-0	0-3	0-0	0-1	0-3	0-2	0-2
Visit 6 (End of Follow-up)*										
N (n†)	13 (1)	17 (5)	15 (0)	14 (1)	13 (4)	26 (0)	12 (0)	28 (2)	10 (0)	18 (2)
Mean	0.1	0.5	0.0	0.1	0.5	0.0	0.0	0.1	0.0	0.1
SD	0.28	1.07	0.0	0.27	0.78	0.0	0.0	0.59	0.0	0.32
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-4	0-0	0-1	0-2	0-0	0-0	0-3	0-0	0-1
Entire Maintenance Phase**										
N (n†)	15 (5)	17 (13)	16 (7)	15 (7)	15 (9)	29 (11)	16 (10)	31 (14)	11 (4)	21 (11)
Mean	1.0	2.1	0.9	0.8	2.2	1.1	1.9	1.0	0.8	1.3
SD	1.69	1.82	1.26	0.94	2.91	2.01	2.42	1.43	1.33	1.83
Median	0.0	2.0	0.0	0.0	2.0	0.0	1.0	0.0	0.0	1.0
Min-Max	0-5	0-6	0-4	0-2	0-10	0-8	0-8	0-5	0-4	0-6

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited opioid typical side effect

Fig. 23 **Sumscores for Elicited Opioid Typical Adverse events at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values**

	Absolute Dose of Naloxone			
Sumscores	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N (n†)	50 (10)	49 (15)	49 (16)	48 (10)
Mean	0.6	0.9	0.9	0.3
SD	1.39	1.67	1.53	0.75
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-7	0-5	0-3
Visit 4 (Maintenance)*				
N (n†)	48 (18)	47 (16)	47 (17)	43 (14)
Mean	0.7	0.7	0.8	0.9
SD	1.23	1.26	1.63	1.94
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-8	0-10
Visit 5 (End of Maintenance)*				
N (n†)	46 (11)	42 (7)	43 (3)	41 (2)
Mean	0.7	0.3	0.1	0.1
SD	1.34	0.63	0.50	0.49
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-2	0-3	0-3
Visit 6 (End of Follow-up)*				
N (n†)	45 (6)	41 (2)	41 (2)	39 (5)
Mean	0.2	0.0	0.1	0.2
SD	0.70	0.22	0.49	0.51
Median	0.0	0.0	0.0	0.0
Min-Max	0-4	0-1	0-3	0-2
Entire Maintenance Phase**				
N (n†)	48 (25)	47 (23)	47 (23)	44 (20)
Mean	1.3	1.2	1.2	1.4
SD	1.67	1.61	1.88	2.27
Median	1.0	0.0	0.0	0.0
Min-Max	0-6	0-6	0-8	0-10

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited opioid typical side effect

Figure 22. Mean Plasma Concentration - Time Curves for Oxycodone Over Time by Treatment - Full Analysis Population for Phamacokinetics